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ARCHIVES OF PEDIATRICS

A MONTHLY DEVOTED TO THE

DISEASES OF INFANTS AND CHILDREN

JOHN FITCH LANDON, M.D., Editor

LEADING ARTICLES IN THIS NUMBER

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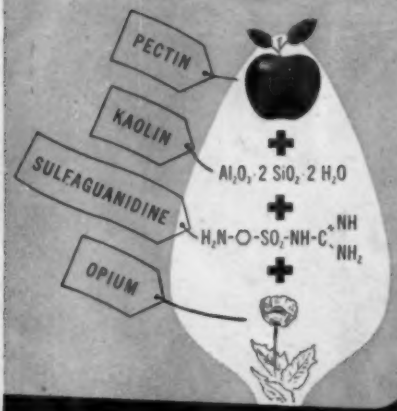

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ARCHIVES OF PEDIATRICS

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INFECTIOUS ORIGIN OF JUVENILE DIABETES

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Ashland, Ore.

The history of the onset of diabetes is easier to trace in children than in adults. John[1, 2] and others have repeatedly emphasized the infectious origin of a large percentage of cases of juvenile diabetes. Although some writers doubt that infection can cause diabetes, there is overwhelming evidence for an infectious origin. This evidence is presented under the following headings: (1) History of infection preceding diabetes; (2) Coma following infection; (3) Seasonal variations of infection and of diabetes; (4) Geographical incidence of infection and of diabetes; (5) Presence of infection in active diabetics; (6) Pathologic findings; (7) Prognosis of diabetes in relation to chronic foci of infection; (8) Treatment of sinusitis and other infections as an aid in diabetes.

1. *History of Infection Preceding Diabetes.* Infection, especially of the upper respiratory tract,[3-5] is probably the most important immediate cause of diabetes as noted by many writers.[1, 6-17] Peterson[18] quoted Senator, Peiper and Stricker as stressing the frequency of colds in association with the onset of diabetes.

A history of acute infection preceding the onset of recognized diabetes is reported in an incidence varying from 15 per cent to 98 per cent as follows: Joslin[12] 15 per cent; Landabura and Magdalena[19] 23 per cent; Toverud[20] 26 per cent; John[21] 32.8 per cent; Fischer[22] 35 per cent; Boyd[23] 56.2 per cent; White[11] 98 per cent. Friese and Jahr[24] found that nearly three-fourths of their sixty children developed diabetes shortly after acute infection. In infants, the preceding infection, as reported in seven cases by Farrell, Hand and Newcomb[25] is febrile and overwhelming.

Case 1. A physician's one-year-old son had a respiratory infection of two weeks' duration. Because of frequent urination, and a five pound weight loss, the child was hospitalized and four-plus sugar was noted in the urine on repeated examinations. The diagnosis of diabetes was confirmed by blood sugar determinations. Diabetes was not present in the parents, grandparents nor in any close relative. The boy, now aged 16, has an active chronic sinusitis and has required large daily doses of insulin since infancy, at present taking 92 units.

The type of infection preceding diabetes includes the acute exanthems, such as measles,[26] scarlet fever,[21] and varicella;[26] mumps;[1, 4, 27] influenza;[1, 4, 25] pertussis;[26] pneumonia;[21] acute colds;[28] and such infectious foci as tonsillitis,[4, 21, 28, 29] and sinusitis.[9, 25, 30, 31] Many of the above infections are complicated by sinusitis which tends to perpetuate the diabetic state.[32] An example of diabetes after scarlet fever follows.

Case 2. A girl, aged 9, who had been treated for sinusitis and pyelitis, developed scarlet fever. She began to lose weight and one month later in coma, she was taken to the hospital where diabetes was diagnosed. Apparently, streptococcus toxin of scarlet fever had injured the pancreas and aggravated her sinus infection. Following insulin, parenteral fluids, antibiotics and treatment of her sinusitis, she convalesced rapidly. She was stabilized on 12 units of insulin in the following year, but required an increased dosage only when colds (exacerbations of sinusitis) developed.

How does infection produce diabetes? John[2] noted the "possibility that the toxemia may exert a direct effect on the islands of Langerhans and decrease secretion of insulin, bringing about hyperglycemia," and glycosuria. Whether the gylcosuria is transient or persistent depends largely on the amount of injury to the islets of Langerhans.[6] Mosenthal[33] believes that "an involvement of the majority of the islands of Langerhans causes diabetes." If sufficient regeneration occurs in the islets, the glycosuria and diabetes disappear.

The interval between infection and the onset of diabetes is often from ten to thirty days.[21]

2. *Coma Following Infection.* Diabetes in children is frequently first recognized by coma.[34] The onset of diabetic coma often coincides with bacterial infection.[8, 35, 36] Perla and Marmorston[37] stated that infection almost always precedes severe acidosis and coma.

3. *Seasonal Variations.* Fewer cases of diabetes begin during the summer months[28] and the disease, once established, ameliorates at this time. Diabetes is more severe during the stormy months of the year, and death tends to occur at this time.[18, 39] Cures of diabetes are not uncommon,[40] improvement during the summer months being due probably to the striking ability of the pancreas to regenerate when the toxic assault on this gland is minimal.

4. *Geographical Variations.* The highest incidence of diabetes exists in climates where streptococcus infections are greatest. On the other hand, diabetes is rare in the tropics and requires little attention to control it.[41, 42] Death rates from diabetes are highest in the North and lowest in the South and Southwest. Comparing countries, death rates are highest in the United States and much lower in eastern and southern Europe, in Central and South America and in Asia.[18, 43]

5. *Presence of Infection in Diabetes.* Sinusitis may initiate diabetes,[9, 28, 31, 44] (Case 3, Fig. 1) and in my opinion, it is probably the most constant source of chronic infection responsible for the chronicity and flare-ups of the disease. It is well known that during a "cold," the insulin requirement may increase considerably.[2, 45] Repeated colds, so common in diabetic children, represent acute exacerbations of a chronic sinusitis.[46, 47]

FIG. 1. Diabetes in youth, aged 23; since age 15, associated with right pansinusitis. Note mouth-breathing and photophobia, secondary to sinusitis.

Case 3. Youth, aged 23, (Fig. 1) was known to have diabetes

for eight years. At age 15, following loss of weight despite a large appetite, sugar was discovered in his urine. High values of blood sugar were noted and diabetes was diagnosed. There was no family history of diabetes nor any preceding acute illness. Patient was always a mouth-breather. He complained of pain radiating into right temple when taking ice cream (symptom denoting ethmoiditis and antritis on the homolateral side[47]). His right sinuses are moderately tender, while his left sinuses are mildly so. Tonsils are small. He is taking 24 units of regular insulin three times daily before meals.

Teed[21] stated: "Some writers have noted a relation between sinus disease and diabetes. It is well known that infections of all sorts may make diabetes worse, and Lierle and Potter[28] noted that juvenile diabetes is frequently discovered first during an acute sinusitis or tonsillitis. They noted, also, that chronic sinusitis and tonsillitis are very common in diabetic children, and recommended that measures to clear these conditions be included in the general management of a case."

Other evidence of infection in diabetics includes an increased sedimentation rate, found by Kramer[48] in 67.8 per cent of 510 tests performed on 366 patients, and an increased capillary fragility.

Increased capillary fragility is the rule in diabetes,[49, 50-52] and is probably due to bacterial toxins. After several years of routine testing with a capillary resistometer on all patients, I concluded that bacterial toxins are the most common cause of low capillary resistance,[53-55] and the production of petechiae.[56] Daeschner and his coworkers[51] reported that 90 per cent of diabetics with increased capillary fragility also had retinopathy. Rodriguez and Root[52] also conclude that increased capillary fragility in diabetics was closely correlated with the development of retinitis and nephritis. Chronic sinusitis, elaborating streptococcus toxins, is a frequent focus for both retinitis and nephritis.[22] Petechiae, spider nevi and telangiectases, which appear in the skin following streptococcal infections[56] resemble early retinal lesions reported in diabetics—"small, round hemorrhages"[51, 57] and "microaneurysms."[51, 58]

6. *Pathologic Findings.* John[1] found definite changes in the pancreas in 96 per cent of 24 diabetic children, and in 95 per cent of 364 adults. In childhood, the majority of cases show hydropic degeneration of the islets of Langerhans, resulting in

hypofunction. The beta cells in the islets, containing granules which are precursors of insulin, are usually partially or completely degranulated, a condition found also in experimental diabetes in rats.[59] Pathologic findings in diabetes may represent the result of injury by bacterial toxins.

7. *Prognosis of Diabetes in Relation to Chronic Foci of Infection.* The strong persistence of the diabetic state may well be due to the relentless attack of toxins on the pancreas. These toxins may have their source in an incurable focus, such as chronic sinusitis and chronic bronchitis, or from repeated respiratory or other infections. I have indicated the importance of chronic sinusitis in many types of chronic toxemia.[32, 46, 53, 56, 60-62]

8. *Treatment of Sinusitis and Other Infections as an Aid in Diabetes.* Diabetic children under my care were examined over many years for foci of infection. Chronic sinusitis and recurrent tonsillitis were the most common. The tonsils were removed, a procedure recommended by Lierle and Potter,[28] and the sinusitis treated.[63] In some of the children, it was possible to discontinue the use of insulin, more often during the warm months. Dean quoted the report of Jeans, that as a result of treatment of chronic suppuration of the sinuses, there has been a decrease in the insulin dosage necessary to control the diabetes.

Antibiotics should be used for acute flare-ups of sinusitis, tonsillitis and other streptococcal infections.[65, 64] Farrell and his associates stated: "Penicillin therapy has favorably influenced the prognosis in infantile diabetes."[45]

DISCUSSION

Only heredity rivals infection as predisposing to juvenile diabetes; the hereditary factor is found in from 25 per cent to 40 per cent. Its role is probably predisposing, while infection seems to be the most common precipitating cause.

The main drawback to the general acceptance of infection as the important cause of diabetes is the impossibility of demonstrating bacterial toxins either in the blood or in the pancreas. Despite the elusiveness of toxins, few would deny that the erythema of scarlet fever or the edema of rheumatic joints is caused by streptococcus toxins, even though they are not demonstrable. Peak amounts of streptococcus toxin in the blood probably explain the frequency of lowest capillary resistance readings obtained in the

spring, in routine testing.[53-55] Streptococcus toxins injure not only the pancreas but effect the pituitary[60] and other endocrine glands, particularly in the spring of the year. Their effect on the thyroid may account, in the spring, for lowest values in the basal metabolic rates of rheumatic children;[65] and their injury to the adrenal cortex may explain why children with frequent colds and active sinusitis have the highest count of lentigines in the spring.[61]

Rheumatic children, both diabetic and non-diabetic, and children with chronic infections, show a high incidence of diabetic-type glucose tolerance curves.[21] Since rheumatic fever in children is probably caused by streptococcus toxins from sinusitis,[62] injury of the pancreas caused by these toxins may explain the abnormal glucose tolerance curves. Some of these children become diabetic after an acute infection,[21] or after continuing low-grade infection.

Treatment of respiratory infections, chronic sinusitis, tonsillitis and other foci of infection may help to prevent diabetes and its complications. John[21] stated: "In view of the large number of cases of diabetes which occur in children after infections, it would be well for pediatricians to examine the urine for sugar once a week for four to six weeks after such an illness. If this were done, diabetes would be discovered early, in many instances, with great advantage to the children concerned."

Among the severe complications, retinitis seems to be related to the duration of diabetes,[51, 57] rather than the adequacy of the diabetic regime.[51, 66] This conclusion may also apply to nephritis complicating diabetes.[67] In both complications (retinitis and nephritis), the initiating factor may not depend upon dietary control, but rather on the persistence of a chronic focus of infection, usually sinusitis.

CONCLUSIONS

1. The most common cause of diabetes in children is a systemic infection which injures the islands of Langerhans.
2. The diabetic state is often perpetuated by repeated upper respiratory infections and chronic sinusitis. Blood-borne bacterial toxins probably prevent regeneration of the injured pancreas.
3. Juvenile diabetes may be prevented largely by control of childhood infections.
4. Treatment of diabetes should include the continuing care of infections, especially chronic sinusitis.

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EFFECT OF ADMINISTRATION OF GLUTEN, STARCH, AND FAT ON CHILDREN WITH CELIAC DISEASE: CLINICAL AND EXPERIMENTAL INVESTIGATIONS. PRELIMINARY REPORT. C. HANSTED. (Ugesk. laeger, 117:481-493, April 21, 1955). The author confirmed the observation that gluten from wheat, rye, and oats is harmful for children with celiac disease, while wheat starch, corn meal, rice flour, buckwheat, peas, beans, potatoes, various vegetables, meat, and fish are well borne. The patient's sensitivity to gluten depends on the kind and amount of fat in the diet. The sensitivity is greatest with a high fat content and greater with milk fat than with olive oil, which consists mainly of triglycerides with unsaturated fatty acids. The clinical symptoms on gluten-free but high fat diet suggest that fat alone may to some degree unfavorably affect children with celiac disease. The gluten sensitivity is the same in a diet free from starch as in a diet rich in starch.—*J.A.M.A.*

ENCEPHALOPATHIES IN EXCEPTIONAL CHILDREN*

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The human brain is estimated to consist of nine to fourteen billion brain cells shaped into lobes of convolutions and fissures. These are connected with each other by strong, thick fibrous mass strands of tissue which form many nerve centers with specific functions, somewhat like an intricate network of telephone circuits, from which thousands of associated nerve fibers emanate connecting all parts of the body, linking them to the principal sensory, motor and reasoning centers in the brain. The brain centers are laced together and to each other in an orderly yet complex fashion. The cells form the brain gray matter; the fiber strands and masses form the brain white matter, also known as neuroglia supporting connective tissue. The gray and white matter of the brain have a rich supply of blood vessels and capillaries and are covered over by three membranous coverings. The brain is protected by a strong cranial bone case and a floating bed of cerebrospinal fluid which protects the brain, blood vessels, and cranial nerves from injury from jarring, trauma, and compression under normal circumstances, during the prenatal developing state, neonatal delivery period, and from postnatal head injuries.

The gray matter of the brain only represents about one-fifth of its contents, while the white matter, or neuroglia supporting tissue, constitutes the other four-fifths. This greater mass, the neuroglia which functions as a transportation system for the entire brain and central nervous system impulses of sensory, motor, memory and reasoning impressions is of vital importance in the structure of the brain, and it became a focal point of research study by biochemists, physiologists, pathologists, and clinicians. It is also interesting to note that in the course of each day's mental and physical work, we use only 15 per cent of our brain functional capacity, while 85 per cent of it remains idle. This leaves us with a huge reserve of brain storage centers of impulses and recollection. It becomes quite a problem at times to understand how we can invade this great mental storehouse in time of need, when areas of the brain are damaged by injury, disease, cerebral

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anoxia, and vascular accidents. As we study our retarded little patients and delve deeply into the etiology of their condition, the pathology and therapy, we have found more and more pathways to their injured brain storage centers, and we are learning how to activate these areas, formerly barred to us, through our clinical and biochemical research efforts. Our brain is an almost perfect mechanism. It requires delicate care and we must nourish it well, bring to it a good daily supply of oxygen, fuel, and energy. This means we must give the rest of the body good care and nourish it properly. Himwich[1] and coworkers found that in the mentally retarded children there is a considerable slowing up of brain metabolism and activity. The normal child's brain consumes 14.2 mgm. per cent carbohydrates from each circulation as compared to 8 mgm. per cent in retardates, and, the normal infant's brain absorbs 8.59 volume per cent oxygen as compared to 3.63 volume per cent oxygen consumed by retarded ones. This is a reduction of about 57.7 per cent, corresponding closely to their low level of intelligence. During the first year of life, the brain increases in weight from 350 grams at birth to 800 grams, and the measurement of the skull grows from 13 inches at birth to 18 inches at one year. It is evident then that, in children in whom this rapid growth and expansion of the brain becomes limited, because of premature ossification of the skull sutures and the smaller circumference of the skull than normal by the first year, brain functions will be limited also, and brain pathology will increase as the compression placed upon it is increased. This is one source of encephalopathy. Before going into the intricate field of encephalopathy, I will explain the beginning and first functions of an infant's brain, compare it to the brain of some of our laboratory animals, which in turn calls for an explanation of the abnormal functions of the brain, and the reason they occur in man.

The late Dr. Frederick Tilney, a close friend of mine, in conversation with me, sometime in 1928, said, "The first message handled by the brain after birth is usually the command to breathe. The infant, free of its mother, suffers from the cessation of oxidation in the blood, and carbon dioxide starts forming. This stimulates respiration. The signal is passed to the diaphragm to contract, to breathe, and a convulsive struggle for air ensues until the breath is taken." Should there be a long interval of cessation of oxidation in the blood and cerebral anoxia occur in the infant for

too long a period of time, a great amount of injury to the brain and its blood vessels can result. This may lead to immediate neonatal encephalopathy, to cerebral palsy and retardation resulting from brain injury, or, an apparently normal looking baby may be born bearing incipient brain damage from residual cerebral anoxia, who may show symptoms mentally of retardation several months after birth. What is the baby's second step or message? The sucking act in nursing or bottle feeding which enables the baby to obtain nourishment. This function brings many nerve-muscle reflexes into play. From now on one may follow the timetable of the baby's growth and development. At one month of age, he lifts his head, turns it from side to side and stares; at two months he smiles; at 3 months notices people who feed him, stretches his hands towards bright colors or follows them with his eyes; at 4 months, he holds his head up, raising it a little and attempts to play with a rattle; at 5 months, he rolls from side to side and may turn over, attempts to sit, and demands attention; at 6 months he sits up in the corner of his crib, and attempts to stand up by grasping the bars; at 10 months he creeps, stands and tries to walk; at 12 months he stands up unassisted, tries to walk alone, grasps a pencil or crayon and tries to scribble. He loses the Moro or hugging reflex which is a prominent sign from 3 to 5 months of age. The mean age for walking is about 13 months, and, at 15 months, he can walk well and has good muscle coordination. He begins to coordinate in play and games. At 18 months, he can climb, throw things around, scribble and play with blocks. At 30 months, he can hop on one foot, run easily, play games well, assort and play with toys. Knowing what the baby should be able to do at the proper age, we can judge, by his inactivity and lag in developmental processes at any given period in his growing timetable as reported by his mother, who observes him closely, with the complaint that he is not like other babies in alertness and play. A thorough history of the case and a neurological examination will reveal the seat of the trouble. In many of these children we find altered functions of the ductless glands which retard cerebral functions and responses, and also body metabolism, growth, maturity, and locomotion. Once a diagnosis of the encephalopathy is established, we can administer rational therapy to the affected child.

It is indeed interesting to compare the infant's early develop-

mental physical and mental responses to that of our laboratory animals. In cats, the first act after breathing is muscular movement which turns it over on its belly, paws on the ground. In from 8 to 10 minutes the kitten crawls to the mother. I believe it feels the heat of its mother's body, and it goes to her for shelter and comfort, and later for feeding. Some call this act, instinct, and with this I cannot concur because when we ice the mother cat's skin, it deters the kittens from crawling to her. When a kitten's paw was pricked with a pin just after birth, it turned over on its back and lay there helpless. Eight days later, the same stimulus causes the kitten to jump up and assume a defensive position. The necessary nerve fibers have been found to be covered by a fully developed and insulated myelin sheath and are ready to function normally. Rats, on the other hand, have no such development at birth. They lie helpless until gathered up into their nest by the mother. They do not take milk for 18 hours after birth. Examination of their brains at birth show there is practically no myelin insulation of any of their associated fibers. Guinea-pigs' brains are almost completely developed, and their associated nerve fibers, insulated with myelin sheathing at birth, are ready to function. We find the guinea-pig's brain almost complete when they are only one day old. This physiological finding in animal experimentation can be applied in principle to the pathology we find in retarded children which is one of immaturity in the development of the brain, central nervous system, and other bodily structures. Demyelinated nerve sheaths are a common finding.

Premature infants are most susceptible to cerebral anoxia, to cerebral pathology and brain lesions. They are liable to respiratory difficulties, especially to the persistence of congenital atelectasis, aspiration pneumonia, and bouts of cyanosis at the slightest provocation. They require meticulous care and handling in incubator oxygen therapy (concentrations below 40), to avoid retrolental fibroplasia and possible blindness; in clearing the throat of mucous, in postural drainage, in correct gavage feeding when necessary, avoid too prolonged oxygen therapy, and avoid infections through careless handling. It is practical to administer water, miscible polyvitamin preparations to prevent vitamin deficiency. They require more caloric values than the normal infant and they do not tolerate fat well. A high protein, moderate carbo-

hydrate, low fat formula is best. Hemorrhages are common in the premature newborn infant, and to prevent this even remote possibility, inject, intramuscularly, 1 mgm. vitamin K soon after birth. The newborn have increased fragility of capillaries and a greater tendency to hypoprothrombinemia, and we may ward off brain injury and damage, as well as a variety of encephalopathies to which they may be subject, by taking extra precautions. Immature brain, central nervous structures, and bodily organs in premature infants are common. Therefore, careful building up and care are essential.

Genetic disorders can manifest themselves at any time of development. Some interfere with prenatal differentiation and some manifest themselves after birth, and even later, as during adolescence and mature life.

Benda,[3] referred to the term, "teratogenic determination" as the science of discovering the exact week or month in which a pathological development had its inception. One may call this "developmental pathology." The *embryonal* period, between the *fourth and seventh week* of pregnancy, when arrests in development will cause septum defects of the heart, oxycephaly, cranioschisis, period of morphogenesis as syndactyly, polydactyly, and abnormal position of the ears. *The neofetal period*, from the *seventh to twelfth week*, is the period of transition in which we get the congenital acromicria syndrome (mongolism), hypertelorism and eye anomalies. *The fetal period* from the *fourth to the tenth lunar month*, or, *period of morphokinesis*, is the one in which we get cerebellar and cerebral agencies, absence of corpus callosum, disorders of differentiation of the central nervous system, microgyria, congenital hydrocephaly, and oligocephaly, as well as vascular anomalies, aplasias of cerebellum, microcephaly, and aplasias of the cerebrum. This knowledge gives us valuable leads which we can utilize in attempting to find the etiological maternal noxious factors that may bring about such developmental blights in the embryo and fetus, and correct them. Biochemical, enzyme, endocrinological and nutritional, vitamin and mineral research have their beacon and searchlights focussed on many of these dark, unknown areas, however, many of these problems, from time to time, are being solved.

We have won brilliant victories over bacterial and viral diseased

infant conditions during the first year of life, but fewer victories have been gained in solving the hereditary forces behind the occurrences of congenital malformations of the brain and central nervous system. A majority of the embryos die very early in the pregnancy and are aborted. MacMahon, Pugh and Ingalls,[3] in 1953, found 18 affected with central nervous system defects out of a total of 339 births or 5.3 per cent, subsequent to the birth of an affected individual, while the expected incidence, were there no hereditary influence, was found to be 0.45 per cent. The observed incidence is approximately six times greater than the expected. Others have found only 2.8 per cent had nervous system defects. The expectancy from the combined studies is about 3.4 per cent. The chance that a mother will produce a second abnormal child in her next parturition is better than 3 per cent. However, the possibility that the next conception will result in a malformed child, or an abortion, is close to 25 per cent. These percentages refer to the more severe types of nervous system malformations. The next question that confronts us is that of consanguinity. Some types of mental retardation depend upon the presence of rare genes recessives in one or the other of the parents. We do find a higher consanguinity rate especially in married first cousins who are the parents of retarded children in contrast to children of a controlled series. In mothers of congenital acromicria syndrome children the possibilities of giving birth to another such infant is slim; it is about 1 in 900, or less. In the familial type or non-mongoloid exceptional child, it is from 1 in 100, or 1 in 200. This implies the presence of a genetic factor exposing the embryo or fetus to an abnormal pattern of growth resulting in cleft palates, harelips, spina bifida, brain and central nervous system malformations. Of these, a high percentage of spontaneous abortions occur from death of the embryo. There may or may not be an environmental factor or factors. In many instances we must search for and diagnose the noxious condition that may be operating in the host during pregnancy preventing the natural protection of the developing fetus from its genes. Properly applied prenatal care may remove the noxious influence and result in a normal pattern of fetal development and growth.

Fortunately, animals can be used to demonstrate the types of deficiencies that produce typical physical deformities and mental

changes. In a hog family, all born of the same mother, a group of six mother pigs, who were deprived of vitamin A in their diets just prior to mating and during their pregnancies, gave birth to 59 little pigs, of which not one had an eyeball. This experiment was carried out by Professor Fred. Hale[4] of the Texas Agricultural Experiment Station at College Station, Texas. Other lesions found in the litters of pigs of the six sows were defective ears, clubfeet, cleft palate, harelip, spina bifida, brain and central nervous system malformations. At a later period, the same six sows were adequately fed with vitamin A good feed and again mated, giving birth to normal litters of pigs without any deformities. Important is the fact that when the blind pigs of the former litters were placed on an adequate vitamin A diet and mated at their mature age, they produced litters of normal pigs with normal eyes and without defects. This is contrary to the tenets of the hereditary transfer of these defects. It can be explained that as a result of better health, vitamin A supplied to the sows and boars before mating, that the sows during their pregnancies through adequate nutrition protected the developing pig embryos and fetus genes to normal growth and litters. In drought periods we suffer serious loss of dairy cattle and sheep herds not only because of starvation but also because of the lack of nutritious green vitamin A rich feed which cripples them. Another report[4] was made, in October 1935, by a farmer in Rolls, Texas, who had litters of 14 pigs born blind. Of these, six pigs were brought to the Texas College Experimental Station for study. It was found that this farmer did not have any green feed available on his farm from March 1934 to May 1935. This condition paralleled the other experimental conditions at the station where the litters of 59 blind pigs were born when the feed was deficient in vitamin A. With the proper vitamin A rich green feed, the six sows gave birth to perfectly normal pigs. Other similarly successful experiments with pigs were carried out at farms in McGlean, Texas with similar results.

The paternal responsibilities were also tested and clearly established. This is another important finding in our clinical prenatal research work carried over from animal experimentation to human improved racial clinical research. In four litters of dachshund pups of four different females sired by the one male dachshund,

who was previously fed a diet deficient in vitamin A, while the females, were fed a nutritious diet, cleft palate, spinal cord and column deformities appeared in one or more pups in each litter. The same bitches, later again were mated with the same dog, both properly fed on rich vitamin A feed, gave birth to litters of healthy pups without any defects. Hence, the entire problem, the role of sex cells which control the body and brain architecture has been largely overlooked. These experiments focus new light on this problem, and new ideas in improved nutrition, of vitamin need in fetal gene protection in prenatal work. It is a very easy matter to place the full responsibility on the mother when defects develop in the children. This data indicates that either parent may contribute directly to certain defects in the children, due to defects in the germ plasm which can be prevented by keeping both parents in normal endocrine balance, by supplementing their supply of fat soluble vitamins, and by good nutrition. A study of families, living in the hill country of North Carolina, was made by Dr. Price[5] who found many cases of physical and mental injury. A typical case was one couple and their only child. The child was so badly injured that he is a mental imbecile. They live on such poor land that even vegetables are scanty in growth and of inferior quality. Their food consisted largely of corn bread, corn syrup, some fat pork and strong coffee. This was one instance of poor living and poor nutrition similar to that of thousands of families observed with children physically and mentally injured.

Moench and Holt[6] of the Cornell Medical School and New York Hospital have made studies of humans and have found a very high incidence of sterility when abnormal forms of spermatozoa reached 25 per cent, and impaired fertility, from 20 per cent to 23 per cent, from sperm head abnormalities. In this latter group, should the affected embryo survive, an imperfect developing fetus and a malformed newborn will result.

The work of Dr. Hector Mortimer[7] and his associates at McGill University, Montreal, Canada, in surgical removal of the pituitary gland of very young rats produced with regularity a defective skull development characterized by lack of development of the facial bones forward of the muzzle with narrowing of the nose and the dental arches. By feeding the animals extracts from the removed pituitary glands, he completely prevented the devel-

opmental defects, thereby establishing the relationship of this injury to deficiencies of the pituitary hormones. Dr. M. M. O. Barrie[8] produced a virtual nutritional hypophysectomy in the young rat by feeding it a vitamin E deficient diet and he noticed a marked degranulation of the anterior pituitary gland structure in the abnormal young, and in the sterile adult animals. We are also familiar with the relationship of hyper- and hypo-secretions, hyperplasia and atrophic changes in the thyroid gland, adrenal cortex, gonads, and pituitary gland due to congenital lesions, tumor, or disease in the brain, central nervous system, in other organ and tissue growth and developmental pathology and altered functions in animals and in humans. We must realize that the nutritional biochemical changes within our body, the bodily enzyme and co-enzyme systems, the transportation system conveying the nutritive products, vitamins and minerals to the tissue cells for intracellular and extracellular fluid and electrolyte balance and nutrition content, must continue in an unbroken line from the daily intake of good nourishing foods, vitamins, and minerals to the oxidative processes in the cells to keep the body organs and tissues in normal development and growth. This applies particularly to couples receiving prenatal care, and then, to their children after birth. Good mental health is founded on a normally functioning body. These normal bodily biochemical processes can only function properly when we have an integral and adequate group of ductless glands in the body co-ordinating its functions with those of the body nutrition biochemical laboratory assembly line. With such co-ordination and good nutrition for the normal body, growth, development, and properly functioning mental processes should be assured.

Practically all metabolic functions are dependent upon, or at least powerfully influenced by the endocrine system. Therefore, changes in the functions of the ductless glands are likely to affect, profoundly, the processes of mental and physical activities. In hypothyroidism, we have a slow down in the basal metabolism, muscular atony, mental apathy, slowing of maturation of the ossification centers, and hence, slowing of linear growth. There is also flattening of the brain convolutions as we find in cretins and congenital acromicria syndrome. Pituitary growth hormone (somatotropin) when in excess increases bone length and width. Adrenal

and testicular steroids in the male, and adrenal steroids in the female influences bone maturation and bone age. A hypophyseal tumor in a prepuberty aged boy may cause no inhibition in gonadotropic hormones but may lead to gigantism, sex precociousness, emotional disturbances and brain pathology. Should the epiphyses close about the adolescence period, then a combination of acromegaly-gigantism develops. Growth will stop and all the features of acromegaly will show. The sella turcica will be enlarged. A pituitary tumor will be in evidence, and signs of mental confusion and lethargy will become prominent. X-ray therapy focussed at the pituitary tumor, if administered early, may be effective. Stilbestrol therapy may help to control excessive growth by checking gonadotropin production. In Cushing's syndrome, or, basophilic tumor of the pituitary, we also have brain pathology and mental disturbances, and concomitant adrenal cortical hyperplasia and hypersecretion. Here too, x-ray exposure of the adrenal cortex and of the pituitary area may help. Large doses of estrogens and androgens may help to suppress the growth hormones. However, in resistance cases, decompression of the tumor may be the only aid. If a tumor also is found in the adrenal cortex, it should be removed unless it is sensitive to roentgen therapy. Froelich's syndrome which is a combination of mental retardation, adiposity, small genitals, and a possible tumor in the hypothalamic area responds well to x-ray irradiation in the pituitary region and to corrective endocrine therapy. Turner's syndrome of multiple congenital defects, mental retardation, short stature, webbed neck, cubitus valgus, and ovarian dwarfism is improved with the use of estrogens in large doses. We find many children with mental retardation and encephalopathy of various degrees in several of the syndromes created by adrenal-genital combined disorders. We may get masculinization of the female with excessive hair growth, and sex precociousness of both sexes with bodily overgrowth and genitals. It may expose them to sex crimes and perversions. Problems of male feminization, and female masculinity are common; sometimes this creates a sex determinant problem in babyhood. A female with a large clitoris may be mistaken for a male, and a male with a small penis and hypospadius may be taken for a female. X-ray therapy to the suprarenal glands may help. Cortisone too may help, but, we must be on the watch for pituitary

depressed function at which point cortisone therapy must be stopped. Another large series of cases among the encephalopathies are the cerebral palsy children.

Children with cerebral palsy number over a million in the United States. It is a condition that requires serious attention from a diagnostic as well as the treatment viewpoint. The clinical varieties of the disorder, which is a brain lesion, either congenital or acquired, is one in which the affected muscles have been released from normal control because of damage to the brain, or to other parts of the central nervous system, or possibly both. They are divided into the spastic lesions found in 65 per cent of the cases, chorea-athetotic syndrome with or without mental retardation in 20 per cent, ataxic children in 8 per cent, rigidity forms in 4 per cent, tremor types in 2 per cent and the atonic and mixed forms in about 1 per cent. The lesions are mainly in the cortex, basal ganglia, hypothalamus-thalamus areas, and the cerebellum and brain stem region. A small percentage have aphasic lesions. In my series of 80 cases of prenatal congenital lesions, neonatal brain injuries from cerebral anoxia, immediate and residual brain lesions, and from postnatal inflammatory and traumatic encephalopathies, all but two children were mentally retarded. This is not the average in such cases. It is only because the more severe types of affected children are referred to me. The children are from 6 months to 14 years of age, the sexes almost equally distributed. In the average cerebral palsy cases, we have about 40 per cent who suffer from epilepsy, over 60 per cent from mental retardation, about 70 per cent with poor speech defects, and about 15 per cent without any speech. The problems of the cerebral palsy children, especially the emotionally disturbed and mentally retarded, are many. It is a difficult task for the parents, and for the community, to cope with many of the situations, and surgery may be indicated for relief. Indicated cases must be carefully selected.

Dr. Samuel Rosner[9] performed craniotomies of ptyrian and suboccipital decompressions on 37 children with encephalopathies. I[10] have been present at most of the operations. Of extreme interest to me was the similarity of the brain pathology we found in all of the operative cases. Upon opening the dura and exposing the brain, it appeared a dull steel-gray color, flattened and pulseless, covered with venous angiomata grouped together like a bunch

of tangled worms. This vascularity found at the lower end of the sylvian fissure branched out feeding into a central venous lake, or into a large central vein. Occasionally we found a central arterial aneurysm, cysts, and arachnoid adhesions which were separated and freed, cysts were excised, and the angiomatous vessels were destroyed with electric cautery. As soon as the brain pressure was released by removing the vascular pathology, the brain changed to a healthy pink color, it became expansile, and alive, pulsating once again. It was fascinating to see this change for the better within a period of seconds. The children's health was checked prior to the operation, and also postoperatively. There was considerable improvement months after the operation. The risk is practically nil. Most of the children began to speak, walk, feed themselves, epileptic seizures ceased or became mild in most of them, and there was a general improvement in mannerisms and intelligence.

A word about the prophylaxis of cerebral palsy children. Since 1922, Dr. William Sharpe[11] reported a means whereby we can prevent moderate to small cerebral hemorrhages in the newborn from becoming potential cerebral palsy cases later in life. He performed spinal taps on 500 newborn infants during the first 24 hours of life at the City Hospital at Welfare Island, City of New York. Of these, 47 infants, or 9 per cent, showed bloody to blood tinged spinal fluid. Daily taps were repeated on the affected infants until the spinal fluid was clear. This averaged three taps per case. The children were followed up for seven years, and not a single case of cerebral palsy appeared among them. According to general statistics, at least 2 per cent of the children should have developed cerebral palsy. In this group, all escaped this fate. Since that time, over 15,000 babies received preventive spinal taps with similar findings and preventive cerebral palsy complications. We should perform prophylactic spinal taps on infants who appear drowsy and show poor suckling ability during the first 24 hours of life. This, to my mind, is prophylactic medical progress of an essential nature in preventing the occurrence of cerebral palsy.

In some of the newborn babies, who appeared normal at birth, months and at times several years later residual cerebral retardation symptoms may show as in cases of cerebral anoxia, in the heredodegenerative diseases or lipoidoses involving abnormal

cholesterol, cerebroside, and phosphatide storage in a group of children, who become markedly retarded, and, in most instances, progressively blind. There are also a large group of congenital lesions such as brain atrophy, brain sclerosis, arrested brain development, intrauterine meningeal and viral infections of the fetus, and, cerebral and cerebellar aplasias where the infant survives fetal development and creates postnatal problems for the physician and the family. Many normal children at any age may develop encephalitis following a contagion, a vaccine injection, vaccination, meningitis, and, pneumonia after which marked symptoms of mental retardation and evidence of brain pathology will appear. If the children stricken with postcontagion and infectious encephalitis and mental retardation are treated early with immune globulin 0.14 cc. per pound of body weight, or, with the method of Bower and Knouf,[12] typhoid vaccine hyperpyrexia therapy, most children will recover completely from the diseased mentation. Another new, hopeful therapeutic agent is the supersonic machine operated by Dr. Fry[13] and coworkers at the University of Illinois, which helps destroy the diseased parts of the brain without affecting any of the normal cells or tissue.

It is not uncommon to find apparently normal individuals, many of them children, following general nitrous oxide or ether anaesthesia, intravenous or spinal anaesthesia who become brain injured through prolonged cerebral anoxia and develop immediate or residual symptoms of disordered mentation with emotional disturbances and mental retardation.

Cyril B. Courville[14] and coworkers for the past two decades did arduous clinical research in studying various phases of the problem of cerebral anoxia as associated with a group of divergent and bizarre lesions of the brain. These investigations have opened the door, little by little, to a broader aspect of the most neglected and least understood of all the anoxias, that of the paranatal variety. It is the unusual type of gross and often deforming cerebral lesion disclosed only, sometimes two years after an apparently normal birth, at autopsy of a paranatal asphyxia baby. Such cases may be mistakenly ascribed to a congenital cause, or to hereditary influence, to encephalitis, to a degenerative process, or less often to a birth injury, or circulatory disorder. These residuals of paranatal asphyxia have but one common responsible etiological factor, anoxia.

LABORATORY TESTS

Essential laboratory tests of the blood and urine should be made to confirm, or, as an aid to diagnosis and as a guide to therapeutic progress. General urine examinations, other chemical tests, including the Sulkowitch calcium test, and microscopic examinations are carried out frequently in each case. Blood chemistry, pH, total cholesterin and cholesterin esters, clotting and bleeding time, blood counts, the differential and hemoglobin, calcium and phosphorous estimation, and nitrogen estimations are also included. The alkali phosphatase, urine 17-ketosteroids, and serum inorganic phosphorous all have significant importance especially in the acromegaly, in Cushing's syndrome, in Marfan's syndrome, in adrenal-genital, and gonadal syndromes, as a guide to therapy and its effects. In indicated cases only should electro-encephalographs, and pneumo-encephalographs be taken. We must not subject our patients to unnecessary tests that involve time and expense, and supply no additional information to the case. The Abderhalden urine endocrine tests give important information to the attending physician. I will dwell on this test procedure in a separate article. Vitamin deficiency tests may be carried out in clinical research and for therapeutic purposes.

In the treatment of the exceptional children with encephalopathies, we must individualize each case. These children show disturbances in perception, thinking, speech, motivity, muscle incoordination, many suffer from petit-mal or grand-mal seizures, catalepsy, night tantrums, and varying degrees of emotional disturbances. A schizophrenic personality is noticeable in many of the children. Endocrine deficiencies can be replenished by corrective glandular therapy such as pituitary calf whole gland (Armour), one capsule daily, which helps the growth and stimulates the maturity processes. Thyroid extract in small doses at first and worked upward to the tolerance point in cases of hypothyroidism is helpful. Large doses of testosterone is helpful in retarded children suffering also from acromegaly. In these cases, x-ray irradiation to the pituitary and adrenals is sometimes helpful, and occasionally, surgical removal of the tumor may become necessary and be imperative. The same holds true in cases of Cushing's syndrome. Cortisone therapy may help the latter in diminishing pituitary secretory activity. Chorionic gonadotropin

may be helpful in association with pituitary calf therapy in Froelich's syndrome children. Here again, because a tumor may be present in the vicinity of the hypothalamus, x-ray exposures to the pituitary area may reduce the size of the tumor and the pressure producing symptoms. The administration of 20 to 30 grams of 1 (+) glutamic acid daily in addition to the glandular correction given to the affected children improved their intelligence from 35 per cent to 50 per cent. In cases of epilepsy, milontin is excellent in the grand-mal and the petit-mal seizures, tridione and paradione may be used as anticonvulsants in petit-mal, and to control myoclonic and akinetic seizures, phenurone in psychomotor types, also mysoline, and gemonil in the mixed types of seizures. The doses will depend upon the age of the child and the frequency and severity of the seizures. Increased doses of vitamin A, vitamin B complex, vitamin C, and Aquasol E I found beneficial to all of the children especially the athetotic, the emotionally excitable, and, the muscular weak and incoordinating group of children. The schizophrenic types of behavior children are helped by administering "histamine diphosphate 0.275 mg. per cc." 0.05 cc. subcutaneously daily, and increasing the dose by 0.05 cc. each day, five days a week, resting each weekend. On reaching 0.5 cc., I keep at this dose for a total period of 16 treatment weeks. It improves the schizophrenic behavior, and, the behavior pattern is closer to the normal. The blood serum pH is lowered, closer to the normal blood-serum of pH 7.25 at which point the behavior is best. At times, sedatives or tranquilizers such as reserpin, thorazine, miltown, reserpoid, and, elixir Gabail in combination with elixir dexedrine and elixir betallin S, in equal parts, given in teaspoon doses every four hours help. The doses of the other preparations such as the reserpin is usually 0.1 mg. twice daily, and the thorazine, 10 mg. twice daily. Sometimes a preparation will help one child, but not the other. We, therefore, have to select the therapy for each child according to the effectiveness and tolerance. It helps to curb the emotional excitement and improves sleep. Antihistamines are very helpful for their anti-allergic properties since many of the children's reactions are of an allergic character, especially the epileptic children. Brain surgery, previously mentioned, is a great help where indicated. Sicca-cell therapy where indicated is another very helpful treatment agent, and it

will be explained in detail in a separate article to appear later. Physiotherapy, speech therapy, and psychological guidance are valuable adjuncts. Proper dietetic care is of vital importance. We must build their frail bodies to an improved health grid, correct many of the endocrine dysfunctions, mature the immature structures, and ameliorate some of the damage to the brain to improved function. The healthier and happier child will behave better and will learn more than the untreated and neglected one, who becomes difficult for the psychologist and the teacher to handle.

I agree with Dr. D. H. Milman[15] who says, "parents need help in scaling their expectation to conform with the child's potentialities, help in learning to substitute their own external control for the child's lack of inner control, help in structuring and simplifying his environment so that he will not be tormented by his impulsivity and distractibility, and help in learning to communicate their acceptance of him, to give him assurance and a feeling of dignity and self-acceptance." Vocational orientation to fit his existing abilities must be sought and be made a part of his training and educational program to prepare him for future security and happiness. Sheltered workshops or trade schools, and recreation centers properly organized and chaperoned will improve the children's opportunities for success in social mixing, relaxation, and for a happy social life similar to that of other children.

I wish to extend my sincere thanks and appreciation to Dr. Hermelinda C. de Varela and Dr. Pedro V. Nunez, President and Secretary respectively of the Pediatric Society of Panama, and, Pediatric Staff Members of the Hospital del Nino, Panama, Republic of Panama, for their assistance during the daily clinic sessions at the Hospital del Nino as well as for their invitation to address the Pediatric Staff at the hospital on April 19, 1956.

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ASEPTIC MENINGITIS: ISOLATION OF COXSACKIE AND UNIDENTIFIED CYTOPATHOGENIC VIRUSES FROM CEREBROSPINAL FLUID BY TISSUE CULTURE METHODS. D. Duncan; A. J. Rhodes; G. A. McNaughton, et al. (Canad. J. Pub. Health, 46:1-8, Jan. 1955). Cerebrospinal fluid specimens from 52 patients with a diagnosis of "aseptic meningitis probable non-paralytic poliomyelitis" were collected in 1952 and were stored in a carbon dioxide "dry-ice" box until 1954 when they were used for the inoculation of trypsinized monolayer cultures of kidney epithelium obtained from rhesus monkeys. Only five of the cerebrospinal fluids yielded cytopathogenic agents. Three of the five were identified as group B Coxsackie viruses; the other two remained unidentified at present, but fell into the general category of "orphan" viruses. Convalescent phase serums were available from all five patients from whose cerebrospinal fluid cytopathogenic agents were isolated. Serologic tests that were performed on these serums showed that in all of the three patients whose spinal fluid yielded group B Coxsackie virus increases in antibody to the homologous strain occurred in convalescence. A definite rise in homologous antibody occurred in the serums of both the patients from whose cerebrospinal fluid unidentified cytopathogenic agents were isolated. There was no evidence from isolation or serologic tests that the patients from whose cerebrospinal fluid viruses were isolated were concurrently infected with poliomyelitis virus. These results suggest that the five patients had aseptic meningitis caused by group B Coxsackie virus or the unidentified cytopathogenic agent. The clinical features of the five patients concerned were those of benign aseptic meningitis and not specific.—*J.A.M.A.*

STILL'S DISEASE

A Perplexing Problem Marked by Pyrexia of Six Years Duration

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The perplexities which accompany prolonged febrility are well-known to all physicians. Those medical men who have repeatedly emphasized the preëminence of data accumulated by clinical observation may find here some vindication for their stand. The mass of data gathered through prolonged laboratory observation did little to add assistance in the arrival at a conclusion for the basic etiology of this prolonged (and actually agonizing) disease complex.

CASE REPORT

Paula L. was born on December 3, 1945 and she weighed 9 pounds at birth. There was little in the way of illness during the first 4 years of life and the photographs of this child in the family album attest to her husky constitution. The parents are each 46 years of age and both have been in good health with the exception of recurrent urinary infection in the mother, who suffered from occasional severe costovertebral pain. The patient's paternal grandfather died of leukemia.

I first saw Paula L. on January 8, 1950, at which time she was found to have a combined infection of varicella and scarlatina. Fever was present to a level of 103° rectally. The infection responded well to penicillin and the child's state of health was rapidly restored. One month later it was noted that the child had fever upon exertion. The response to rest in bed was consistently good, and antibiotics were not employed since abnormal physical findings were lacking. Febrility became a rather predictable factor as a concomitant of exertion and fatigue. Paula developed profuse vomiting with girdle pains on July 29, 1950. Rectal temperature level was 101.6°. Physical examination was entirely negative except for costovertebral tenderness bilaterally. Repeated microscopic examinations of the urine were negative. It was necessary to use opiates in the control of the pain which lasted for three days. It was again noted that a consistent elevation of temperature (101.8° to 103.2° rectally) would occur following exertion. I did not feel

at any time that this child suffered from "thermometer disease" since I had on many occasions confirmed the fact that the little girl *would develop elevation of temperature to an abnormal degree after rapid walking or cycling.* She appeared ill with bouts of pyrexia but physical examination was negative rather routinely. There was no retardation in the growth of the patient who during January of 1951 (at the age of 5 years) was 44 inches tall and weighed 47 pounds.

Generalized muscular pains and epigastric cramping were noted during the spring of 1951. Pressure over the affected muscle groups did not intensify the discomfort. The blood pressure readings were consistently normal. A trichanosis skin test was negative. The epigastric cramping became more marked and later precordial pain became a problem as well. The child became pale, apathetic, and could no longer attend school. Fever to 102° rectally was noted in the afternoon and evening. A chest roentgenogram, intravenous pyelograms, and later, retrograde pyelograms were found to be normal. Repeated urinalyses were made and finally one specimen was found to contain 40-60 WBC per hpf. The "girdle pains" persisted after the urine was cleared of pus by the use of sulfonamides. Porphyrinuria was suspected but excluded by laboratory means. The patient had not been in contact with any individual suffering from precordial pain.

Paula complained of constant epigastric pain. Blood counts, erythrocyte sedimentation rates, and visualization of the gastrointestinal tract showed no abnormality. There was no response on the part of the child to various antispasmodics.

Laparotomy was performed on September 22, 1952 and only a moderate degree of mensenteric lymphadenitis demonstrated. The chest x-ray showed some scattered calcific change in the hilar regions. The tuberculin test was negative, but the histoplasmin skin test was strongly positive. Bone marrow specimens were found to be normal both from the cytologic and cultural standpoints. Stool specimens were negative for ova and parasites. Skull roentgenogram was negative.

The patient began to complain of numbness in the lower extremities and even minimal exertion was accompanied by febrile spikes to as high as 103° rectal. Chills and breathlessness became a part of her pattern of symptoms and were particularly noted

with exertion. She was admitted to the Methodist Hospital, Indianapolis, Indiana, on December 18, 1952 for further observation. Physical examination was negative except for a mild vaginitis. The blood pressure was 105/65. The hemoglobin was 14 grams for each hundred cubic centimeters of blood. The erythrocyte count was 4.5 M, and the WBC 6.1 T for each cubic millimeter of blood. The clotting time was three minutes. A differential count was normal. The urine contained 30-40 WBC per hpf. Cystoscopic examination showed the bladder neck to be hyperemic. Retrograde pyelography was normal and urine obtained from the ureters was clear. She was treated with terramycin.

The child thrived physically but her symptom complex was as profound as ever. Her pallor was obviously reflex in nature and not based upon anemia. It is rather startling for me to recall the amount of time which I daily allotted for the express purpose of "grinding" over the case of Paula L. The time honored method of "forgetting" all that I knew about her and starting afresh had been sadly abused. Doctor William N. Wishard, the urologist, and myself always found ourselves discussing Paula when we met for the discussion of any current problem. We were both convinced that we dealt with a systemic disorder, the nature of which had totally eluded us.

Paula's parents were called to the office and the problems which she presented were discussed. They accepted my recommendation of taking her to an outstanding clinic here in the midwest for another opinion as to the nature of her illness. This was done on August 20, 1953. The findings were much as has been outlined. The blood count, erythrocyte sedimentation rate, urinalysis, blood urea, skull and chest roentgenograms, and retrograde pyelography were all within normal limits. The histoplasmin skin test was strongly positive. A definite conclusion as to the basic nature of the illness could not be reached.

The patient returned home and was observed periodically. The Bence-Jones protein determination was negative as were the erythrocyte sedimentation test and repeated urinalyses. Urine cultures for acid-fast organisms were negative. Pericarditis was suspected because of attacks of heaviness in the upper chest accompanied by palpitation. Some of these attacks were accompanied by erythematous reaction in the skin. Pruritis was present. Examination

of the heart was negative as was an electrocardiogram. Blood cultures were reported as showing no growth. An orthopedist saw her during December of 1953 and could find no musculoskelatal defect.

Paula was 56 inches tall and weighed 95 pounds at the age of 10 years. She appeared in good health yet walked rather stiffly due to severe pain in the upper tibial areas. She was seen on January 23, 1956 because of inability to walk. There was generalized joint stiffness and muscular tenderness. The marked disability in walking was due to pain and tenderness in the hips. Generalized lymphadenopathy was present without splenomegaly. The pain and stiffness in the hands receded for 48 hours, but recurred and were accompanied by joint swelling in the fingers as well as in the ankles. The temperature was 103° rectally and the leukocyte count was 9,250 per cubic millimeter of blood with normal differential. The erythrocyte sedimentation rate was 12 mm. per hour. The antistreptolysin test was reported as normal (12 Todd units) and the C-reactive protein was negative. Treatment with cortisone was helpful in bringing about the resolution of pain.

Paula L. is a strongly built blonde girl who on March 15, 1956 was found to be 57 inches tall, and who weighed 97 pounds. She had been observed for a period of six years during which time she suffered from a myriad of symptoms so bizarre at times as to suggest a smouldering systemic disorder. Episodes were noted which suggested "borrowed" complaints yet, in retrospect, it is reasonable to accept the fact that the whole complex of symptoms and signs evaded both clinical and laboratory definition.

The final impression would of necessity have to be Still's Disease.

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PEDIATRICS AT THE TURN OF THE CENTURY

From time to time the Archives, which was the first Children's Journal in the English language, will reprint contributions by the pioneers of the specialty over fifty years ago. It is believed that our readers will be interested in reviewing such early pediatric thought.

GRIP MENINGITIS*

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Washington, D. C.

At 6 P.M., January 1, 1907, I was summoned to see E. S. M., male, white, five years old, American, because he "had bitten off the bulb of a thermometer." It was noticed by his nurse, a competent French woman, that he ate very little luncheon, but he was taken in his pony cart to the Zoo. Here he took no interest in the animals, but seemed to be unusually quiet. Upon reaching home at 5 P.M., he seemed "drowsy and feverish," so his nurse attempted to take his temperature orally, as she had frequently done, when his jaw quivered and he bit the thermometer. The pieces of the thermometer were fitted and the parents were assured that he had swallowed neither glass nor mercury. As he seemed very drowsy and hot, I took the rectal temperature, which was 106.4° F. His mother expressed the belief that he had an attack of indigestion, such as he had had many times, and I concurred in this opinion, as there was no evidence of organic disease. I gave him a tablespoonful of sodium bicarbonate in a quart of warm water by rectum, which he retained for more than an hour; it was then passed and was slightly colored by fecal matter. He was also given a bath at 100° F. for ten minutes. At midnight his condition had not improved, and the treatment was repeated, but without effect upon the temperature or bowels. He was also given calomel, gr. j., resorcin, grs. ij., in ten divided doses.

January 2, A.M. He had been vigorously treated by baths during the night, but his condition had changed only slightly. Temperature was 106° F., pulse 140, respiration 36. Considering the high temperature, his intelligence was good and he begged for his breakfast. The idea of indigestion was now dispelled and I ex-

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cluded cerebral, cardiac, pulmonary, gastroenteric and urinary diseases, and expressed the belief that the child had a severe attack of grip with such cerebral manifestations as are usual with hyperpyrexia. After impressing upon the parents the gravity of the condition, attention was directed to controlling the temperature by ice cap and sponge baths, to feeding and to the administration of a mild febrifuge. The temperature gradually subsided during the day and fell to 101° F. by 10 P.M. He had been restless, gritting his teeth, and showed only slight improvement mentally. His urine was normal.

January 3, A.M. Had a very restless night. Had several dark stools. Was sponged every two hours. Complained of headache and of being tired. Temperature reached maximum of 105.2° F. during day. Restless, gritting teeth; pain in back of neck; cried out when moved; headache and talked to himself.

Dr. W. D. Booker in consultation at 5 P.M. confirmed diagnosis of grip. He also attributed cerebral symptoms to high temperature.

January 4, A.M. Condition unchanged. During day temperature at lower range, but nervous symptoms remained the same. At midnight, he seemed more comfortable.

January 5, A.M. Two chills during night, one at 1 A.M. and the other at 3 A.M.; temperature reached 105° F. A third chill at 5 A.M. Restless and talked in sleep. Constantly complained of being cold. Answered questions intelligently and politely. At noon had a chill. 3 P.M., Dr. W. S. Thayer was called in consultation. He also agreed with the diagnosis and the treatment. During the past twenty-four hours the child had been given 2 grains of quinine every three hours, and, as there was a remission in the temperature, it was thought best to continue it. Early in the afternoon Dr. E. B. Behrend examined the blood and reported as follows:

Red blood cells	4,250,000
Leukocytes	10,800
Hemoglogin	90%
Color index	1.05
Differential count:	
Polymorphonuclears	88%
Small lymphocytes	10%
Large lymphocytes	2%

Stained specimen showed nothing of pathological importance. Malarial parasites absent. Attention was directed to a slight earache which the child had for a few minutes several days prior to his illness. I thereupon asked Dr. Joseph H. Bryan to meet me at 6 P.M. He found the left drum normal and a slight redness of the right, but expressed the positive opinion that there was neither middle ear nor mastoid disease, nor did he believe the ear had anything to do with the condition. However, he suggested having the ear irrigated frequently with a warm normal salt solution, which was done.

January 6, A.M. Slept quietly about ten minutes at a time. Three chills during the night, temperature reaching 105.4° F. As yet no positive symptom of meningitis had developed. There had been no muscular twitchings and the pain in the neck had abated. The child answered questions, seemed to know different persons, but was excited and talkative.

Noon. In consultation, Dr. Thayer called attention to the beginning of Kernig's sign, but an absence of every other symptom indicative of meningitis. Dr. Bryan pronounced the ear better and reassured us that it was not causing the trouble. Dr. Wilmer said the eyes were normal and presented no evidence of brain disease. There was noticed an exaggeration of a congenital internal squint of the left eye.

The consultation confirmed the diagnosis that had been made the second day of the illness.

P.M. Two chills during the afternoon and very restless.

January 7, A.M. There was but little change in his condition. He became so restless and noisy during the night that Dr. Grasty, who was watching him, ordered morphine sulphate gr. $^1/_{10}$, hypodermatically, which quieted him for several hours.

In consultation, nothing more positive was determined; Kernig's sign was a little more marked, though there was no other manifestation of meningitis. Stupor more marked, not intelligent, nor did he recognize anyone, and there was some doubt about his seeing objects, although occasionally his eyes followed the candle. Defecation and urination involuntary.

January 8, A.M. Condition worse. Two chills.

Noon. Consultation. Symptoms of meningitis were now present, such as marked Kernig's sign, ankle clonus, retracted head, congestion of the fundus of the eye, and coma. It was now agreed

to do a lumbar puncture, so at 4:30 P.M., with the assistance of Drs. Behrend and Prentiss Willson, I drew off two ounces of cerebrospinal fluid, which was examined by Dr. Behrend. His report read as follows:

Two ounces of fluid were obtained from the spinal cord by lumbar puncture. This was quite turbid, and there was an immediate deposit of thick viscid pus. A smear made from the pus contained a large number of small delicate bacilli which were partly free and partly enclosed within the leukocytes. As many as eight or ten were found in some of the cells. The free bacilli were single, arranged in short chains, end to end, the smallest appearing as diplococci, so that the first impression was that we were dealing with a mixed infection. This appearance of diplococci was due to the selective or polar staining of the organism.

The ordinary laboratory media, including human blood agar, were inoculated with the pus. There was no development after forty-eight hours on any except the blood serum and human blood agar.

On blood serum there were fine glistening pin-point and colorless drops. On the blood agar there were fine glistening dot-like points larger than on the blood serum, discrete and translucent. Here and there were a few areas where the colonies became confluent. Under the low power they were round with sharp outline, glass clear and not granular. Subcultures from the blood serum and blood agar failed to grow. Cultures made from the spinal fluid forty-eight hours after removal failed to develop. Smears made from the cultures showed the presence of many small rods about one-quarter the size of a red blood corpuscle. There were also a number of quite large bacilli, much larger than the size usually attributed to the grip bacillus, frequently slightly curved, with a tendency to polar staining. The organism did not take Gram's stain. The bacilli were not motile, and grew only at the temperature of 37° Centigrade.

A careful consideration of the cultural and staining qualities of this organism leads to the conclusion that we are dealing with the bacillus of influenza. The diplococcus-like forms and the rather long rods found now and then are not quite in accordance with the typical description, but have been noted by other observers (Mallory and Wright). With this exception, it corresponds with everything that is known of Pfeiffer's bacillus.

In two or three hours after the removal of the fluid there was a perceptible improvement in the child's condition. He recognized the voices of his brother and sister, took his treatment with less agitation and his temperature fell 3°. This abatement encouraged those about the bedside, but it was explained that it would probably not last long.

January 9, A.M. As had been predicted, he became worse during the night, had a severe chill which lasted half an hour and the temperature rose to 106.2° F. By noon, he was so much worse that I yielded to the entreaties of his mother, and, with the same assistance, drew off one ounce of cerebrospinal fluid. This procedure was not well borne, and he collapsed.

6 P.M. In consultation, the child was now considered to be *in extremis*, but Drs. Behrend, Willson and I thought the bad symptoms might be attributed to the lumbar puncture.

January 10. Slight improvement in the morning and much brighter than the previous night. When drops were put in his eyes, he felt in his pajama pocket for his handkerchief, then wiped his eyes with his hand. During the afternoon he had a chill, lasting one and one-quarter hours; his temperature was 105.2° F.

January 11. Had a fair night, but his respirations increased in the morning. During the day, he was kept alive by free stimulation, by hypodermoclysis and rectal injection of salt solution. Death came at 9 P.M.

Throughout the attack, the boy had been kept on liquid food, and stimulation was withheld until the last few days of life.

For the last six days of the illness, a physician was in attendance day and night, so that every change was observed and intelligently treated.

The reasons for making the diagnosis of grip after the first twelve hours were:

1. Other members of the family were recovering from it.
2. The patient had had a slight attack a week or so prior to this illness.
3. Other conditions which might have produced similar symptoms were excluded.
4. The course showed profound toxemia.

I am indebted to Dr. Prentiss Willson, of this city, for examining the literature of this subject and tabulating the published cases.

That meningitis has been recognized clinically as an occasional

complication of influenza, especially since the pandemic of 1889-90, no one will deny, but in only a few cases was the diagnosis based upon bacteriological findings. In this paper only such cases as were confirmed by finding the microorganism in the cerebrospinal fluid or in the scrapings from the meninges are tabulated. As Pfeiffer described the organism which bears his name, and which is now accepted as the cause of influenza, in 1892, it is evident the diagnosis of influenzal meningitis could not have been made with certainty prior to this time.

In 1902 Ghon reported two cases of meningitis caused by Pfeiffer's bacillus and also reviewed the cases already reported. He found 27 published cases, but in only 10 was the bacteriological evidence sufficient to warrant a positive diagnosis.

The first case was reported by Högerstedt in 1895, that of a man, aged fifty-one. There was no lumbar puncture; cultures taken from the meningeal exudate at the necropsy contained Pfeiffer's bacillus, associated with other organisms not specifically described.

Pfuhl, in 1897, reported a case in which the diagnosis was accepted by Ghon. Male, twenty-two years of age, upon whom lumbar puncture was performed. Cultures made from the exudate taken after death showed the Pfeiffer bacillus associated with the pneumococcus and the streptococcus. Headke was the first to demonstrate that Pfeiffer's bacillus alone could cause meningitis. Lumbar puncture was made on a youth, aged eighteen, who had been ill five days. The operation was performed twice, but no organism grew on the culture, probably because blood agar was not used. Subsequently, cultures obtained on blood agar from the meningeal exudate showed Pfeiffer's bacilli. Cocci were also present, but were attributed to postmortem infection. In 1898 Fraenkel reported two cases in which the Pfeiffer bacillus was the only organism found. Lumbar puncture was not done, the diagnosis being made by cultures from the meningeal exudate. The first case was made in a male infant ten weeks old, and the second, also a male, aged nine months. The duration of the disease was in each case one month.

In 1899, Slawyk performed lumbar puncture twice upon a boy aged seven months. In this case Pfeiffer himself found the bacillus in pure culture. Duration of illness, fifteen days. Meunier's case, a girl aged sixteen months, terminated fatally after an illness of eleven days. There was no lumbar puncture, but Pfeiffer's

bacillus was found in pure culture from meningeal exudate, from a focus of pneumonia and from the pleural surface.

In Peucker's case, a girl, aged five months, there was no lumbar puncture, but Pfeiffer's bacillus and a staphylococcus were obtained from cultures of the meningeal exudate.

Langer's case, a boy, aged nine years, recovered after an illness of twenty-seven days. Lumbar puncture was done and Pfeiffer's bacillus grown in pure culture.

Trailescu's case, a girl, aged six months, died after an illness of ten days. The fluid drawn by lumbar puncture showed Pfeiffer's bacillus in pure culture.

After reviewing the cases given above, Ghon reported two cases. The first was a man, aged thirty-three. The meningeal exudate showed the Pfeiffer bacillus and a streptococcus. In the second case, a boy, aged eight months, lumbar puncture was performed once and Pfeiffer's bacillus was found in pure culture. The child died in ten days and the same organism was found in a focus of pneumonia.

In 1897, Testevin reported the following case, which Ghon had overlooked. A man, aged twenty-three, who had Pott's disease, developed meningitis and the cerebrospinal fluid obtained by lumbra puncture showed the Pfeiffer bacillus in pure culture. He lived six days.

To Testevin would seem to belong the credit of having first demonstrated the presence of the Pfeiffer bacillus in the cerebrospinal fluid taken by lumbar puncture from a case of meningitis.

Hunter and Nuttall, in 1901, in a paper detailing the bacteriological findings in the cerebrospinal fluid obtained by lumbar puncture from 9 cases of meningitis, found the Pfeiffer bacillus in 3. In all of the 9 cases intra- and extra-cellular diplococci were found. In the second and fourth cases there was also present an organism, which they considered the influenza bacillus; also in the eighth case the same germ and a large capsulated bacillus were associated with the diplococcus. All were boys, aged respectively three years, four months, and one year.

In 1902, in addition to the cases reported by Ghon, two reports valuable to the literature of this subject were made by Simon and Dubois. Simon's case was a boy, aged seven months, upon whom lumbar puncture was performed four times, and Pfeiffer's bacillus found in pure culture. The child lived about six days. An interesting account of the bacteriological and postmortem examinations of this case is given in detail.

Dubois' thesis is probably the best consideration of the subject. He translates into French the cases reported by Haedke, Fraenkel, Slawyk, Langer, Trailescu and by Ghon, in which the organism was present in pure culture, and a full quotation of the cases originally reported in French by Testevin, Meunier and Simon. Dubois' case was a boy, aged four months, the duration of the disease being fifteen days. The cerebrospinal fluid, obtained by lumbar puncture, showed the Pfeiffer bacillus in pure culture. The child died

In 1903 Mya reported 4 cases. In his first communication 3 cases were presented. The first was a girl, aged eight months, who, when first brought to the clinic, had an area of bronchial breathing at the base of the left lung, in addition to meningeal symptoms. Three lumbar punctures were made and the fluid withdrawn showed the influenza bacillus in pure culture. Duration of illness, twelve days. Death.

The second case was a boy, aged one year, who had been transferred from the surgical ward upon the development of meningeal symptoms. He had a suppurating arthritis of the right shoulder joint. Lumbar puncture was made once and the fluid showed the bacillus of Pfeiffer in pure culture. Death five days after the first evidences of meningitis.

The third case was seen in consultation. A boy, aged nine months, was taken with meningitis about the middle of June. He also had a bronchopneumonia at the left base, a corneal ulcer, a suppurating otitis of the left ear, and left facial paralysis which antedated the otitis by more than two weeks. The fever subsided about the first of August, but emaciation progressed until the middle of September, when he was reduced to profound cachexia. He gradually improved after this, although left facial paralysis and partial right hemiplegia were present. Three lumbar punctures were made and a total of 105 cc. of fluid was withdrawn. The Pfeiffer bacillus in pure culture was found.

In his second contribution, also made in 1903, Mya reports the case of a boy, aged one year, who was first brought to his clinic for a fall which caused a hematoma of the scalp, in the right occipito-parietal region. Fracture was not detected, and, there being no nervous symptoms, the child was sent home. He was brought back in about two weeks, with bronchopneumonia associated with meningeal symptoms. There was also suppuration of

the hematoma. Lumbar punctures and also punctures of the pneumonic area and the hematoma were made. The fluids from the three localities showed the Pfeiffer bacillus in pure culture. The child died and a lineal fracture in the right occipito-parietal region was found. Mya expresses the opinion that the primary focus of infection in this case was the lung, a secondary infection of the pre-existing hematoma, and then of the meninges taking place. In concluding the paper the author expresses the opinion that Pfeiffer's bacillus is as much of a factor in the production of cerebrospinal meningitis as the diplococcus or pneumococcus, especially in infants.

In 1904 Jundell also reported 2 cases. The first case, a girl, aged eight months, terminated fatally in twenty-two days. The fluid drawn by lumbar puncture showed the Pfeiffer bacillus in pure culture.

The second case, aged eighteen months, ended fatally in sixteen days. Lumbar puncture was not performed, but the influenza bacillus was found in the meningeal exudate obtained at the necropsy.

Thomesco and Gracaski reported a most interesting case in 1904. A child, aged seven years, recovered in ten days. The fluid obtained by lumbar puncture showed the Pfeiffer bacillus. Unfortunately, the original article could not be consulted, the publication not being in the Surgeon-General's Library at Washington, D. C. The facts are, however, taken from an abstract published in a French journal.

The last case found in the literature was reported by Douglas in 1907. A girl, aged ten months, died after an illness of eight days. The Pfeiffer bacillus was found in pure culture in the fluid removed by lumbar puncture and in the meningeal exudate obtained at the necropsy.

It will be seen that 19 of the reported cases[8] were in children, of whom 16 died. Lumbar puncture was performed during life in 17 cases and the diagnosis was definitely determined by finding the bacillus in pure culture.

In conclusion, it may be stated that my case is the first case of grip meningitis reported by an American in which the diagnosis has been confirmed by finding the Pfeiffer bacillus in pure culture in the cerebrospinal fluid removed by lumbar puncture during the life of the patient.

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